

## ORIGINAL ARTICLE

# Determinants of neuropsychological and behavioural outcomes in early childhood survivors of congenital heart disease

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Supplementary tables are available at <http://adc.bmj.com/supplemental>

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**Aims:** To evaluate the relative effect of cyanosis, surgical interventions and family processes on neuropsychological and behavioural outcomes in 4-year-old survivors of serious congenital heart disease (CHD).

**Methods:** 90 children with a range of cyanotic and acyanotic conditions, who underwent either corrective or palliative surgery, completed a neuropsychological and behavioural evaluation. Families of participants were also profiled by evaluation of maternal mental health, worry, social support, parenting style and family functioning.

**Results:** Compromised neuropsychological outcomes were associated with a combination of cyanotic conditions and open-heart surgery, but this was not exacerbated by having a complex, palliative, status. Both cyanotic and acyanotic conditions were associated with specific sensorimotor delays, regardless of method of the correction. Only children with complex conditions and palliative interventions seemed at risk of poor behavioural outcomes; indeed, children with cyanosis with complete repair showed favourable behavioural outcomes compared with controls. Multivariate analyses highlighted the sometimes greater relevance of family processes (eg parenting style, maternal mental health and worry), rather than disease or surgical factors, in predicting especially behavioural outcomes.

**Conclusions:** The findings (1) suggest a more complex relationship between cyanosis, surgical methods of correction, neuropsychological and behavioural outcomes than previously charted, (2) highlight that family processes may be aetiologically more important than disease and surgical factors, and (3) indicate specific targets for secondary prevention programmes for this at-risk population.

An emerging view suggests that children with cyanotic congenital heart disease (CHD) who have undergone surgical procedures involving circulatory arrest are at particular risk of both neuropsychological and behavioural problems.<sup>1–5</sup> However, some studies have found no such evidence or indeed, in terms of behavioural adjustment, suggested better outcomes than controls.<sup>6–8</sup> Moreover, where statistically significant differences have been found, clinical significance is sometimes dubious. Indices of intellectual functioning and behavioural adjustment in some studies have often been well within the normal range, with statistical significance sometimes determined by above-average scores in control groups.<sup>3, 9, 10</sup>

Contributing to this ambiguity, studies have often used restricted samples of children with CHD (eg cases of transposition of great arteries) and have neglected to examine the mediating effects of maternal and family factors, which can covary with CHD.<sup>6, 8, 11–13</sup> This study includes measures of maternal adaptation and family functioning, in addition to cyanosis and surgical factors, in examining determinants of neuropsychological and behavioural outcomes in 4-year-old survivors of severe congenital heart defects. Children with cyanosis are divided into subgroups of those who had corrective versus palliative surgery only. These subgroups have often been merged in previous studies, but important differences are likely. Children without acyanosis are also subgrouped into those who underwent open or closed surgery. In this way, the importance of surgical procedures involving cardiopulmonary bypass,

independent of cyanosis, may be considered. Neuropsychological and behavioural profiles across groups are first considered, followed by multivariate analyses of outcome determinants.

## METHODS

### Participants and groups

Four-year-old children and their families were recruited over a 3-year period from a regional centre. This age group was chosen, as some families later participated in an early intervention trial to promote child and family adjustment at a key developmental period (ie start of formal education). Eligibility criteria included having undergone at least one invasive procedure for correction or palliation of a major heart defect. Children with developmental or psychiatric syndromes were excluded. Of the 149 families invited, 90 agreed to participate. Participants did not differ from non-participants in terms of age, cyanotic status, surgical procedure, correction or palliative status, or socioeconomic status as measured by Townsend Index scores.<sup>14</sup> All were assessed in the 36 months before starting formal education. Mean age at time of assessment was 4.6 years (standard deviation (SD) 0.3; range 4–5.1 years) and mean time since main operative procedure was 3.8 (SD 0.9) years.

**Abbreviations:** CBCL, Child Behaviour Checklist; CHD, congenital heart disease; NEPSY, developmental neuropsychological assessment; WPPSI, Wechsler Preschool and Primary Scale of Intelligence

Four groups were defined by diagnosis and surgical procedure as follows:

- *Acyanotic-closed* ( $n = 34$ ): acyanotic conditions corrected by closed-heart surgery or an interventional catheterisation (eg coarctation of aorta)
- *Acyanotic-open* ( $n = 25$ ): acyanotic conditions corrected by open-heart surgery (eg ventricular septal defect, atrial septal defect)
- *Cyanotic-corrected* ( $n = 19$ ): cyanotic conditions corrected by open-heart surgery (eg transposition of great arteries, tetralogy of fallot)
- *Cyanotic-complex* ( $n = 12$ ): cyanotic conditions and combinations of conditions for which only palliative open-heart surgery was possible (eg hypoplastic right and left heart conditions, double inlet left ventricle).

The four groups did not differ significantly in terms of age, sex, weight, parental marital status, socioeconomic status, parental qualifications or family size (supplementary table A at <http://adc.bmjjournals.com/supplemental>). As expected, the cyanotic-complex group had had more surgical procedures than the other groups (supplementary table A).

For analyses involving behavioural outcomes, an additional mild control group ( $n = 19$ ) of children who had been diagnosed with mild, self-correcting, heart defects (eg small ventricular heart murmurs and patent ductus arteriosus) in infancy were recruited. Although they were slightly older than the clinical groups at the time of assessment (mean age 5.1 (SD 0.3) years; range 4.9–5.2 years), exploratory analyses confirmed that age did not exert an independent effect on behavioural outcomes. They did not differ from the other groups in terms of the other demographic variables described earlier. For analyses involving neuropsychological outcomes, the acyanotic-closed group (presumed to be without major neurological risk as neither cyanosis nor open-heart surgery applied) served as a control group for statistical analyses, in addition to the comparisons made with the clinical norms for the scales used.

Recruitment and study procedures were approved by the local research ethics committee for the region, and families were recruited by letters of written informed consent.

### Outcome measures

Summative IQ scores may be misleading by not detecting deficits in specific cognitive processes or domains. Consequently, five neuropsychological domains were assessed using factor scores from the complete 3–5-year-old version of NEPSY–A *Developmental Neuropsychological Assessment*.<sup>15</sup> These included attention, language, sensorimotor, visuospatial and memory skills. Five additional domains were assessed using specific subscales from the Wechsler Preschool and Primary Scale of Intelligence (WPPSI-R.UK).<sup>16</sup> These included (with scale names added for reference) verbal reasoning (similarities), non-verbal reasoning (block design), social reasoning (comprehension), cognitive speed (coding) and number skills (arithmetic). NEPSY factor scores have a reference group mean of 100 (SD 15), and WPPSI subscale scores have a reference group mean of 10 (SD 3). Tests were conducted with child participants on a one-to-one basis by chartered clinical psychologists, trained in neuropsychological evaluation and blinded to the diagnostic status of participants at the time of assessment.

Behavioural functioning was assessed by scores on the maternally completed Child Behaviour Checklist (CBCL).<sup>17</sup> This study used the composite total problem behaviour index score from this screening inventory for behaviour problems. The

percentage of each group who fell within the clinically significant range of the scales was also recorded.

### Predictor factors

The effect of cyanosis, surgical interventions, palliative status and combinations thereof was assessed through group comparisons as described above. Length of time on cardiopulmonary bypass was additionally recorded from surgical records. In addition, family factors were assessed by having mothers complete several scales. Maternal mental health was assessed using the Brief Symptom Inventory.<sup>18</sup> The composite “general severity index” score was used in analyses here. Maternal worry about the child’s health status—which previous research has suggested may vary independently of actual illness severity<sup>4</sup>—was assessed using the Maternal Worry Scale.<sup>19</sup> The Parenting Locus of Control Scale<sup>20</sup> was used to profile the parenting style. Four of the five subscales were used to measure the degree to which parents hold beliefs and practice parenting behaviours that are likely to be effective in terms of child behaviour management and adjustment. Family functioning was assessed using selected subscales from the Family Environment Scale.<sup>21</sup> Four subscales (45 items) were used which rated familial cohesiveness, conflict, expressiveness (open and direct communication styles) and extent of active or recreational family activities. Finally, social support available to the family was evaluated by the Significant Others Scale.<sup>22</sup> This measure assesses the quantity and perceived quality of available social support, and two indices were used that reflect the degree of “emotional” and “practical” social support.

Socioeconomic status was measured as described earlier,<sup>14</sup> and additional family and demographic factors (highest parental qualification, marital status, number of siblings, age and sex) were reported by mothers before psychometric assessment.

### Statistical analysis

The data satisfied statistical assumptions for parametric analyses. Multivariate or univariate analyses of variance were used to compare group means on neuropsychological and behavioural outcomes for statistical significance. Effect size deviations from reference means were used to assess the clinical relevance.<sup>23</sup> Half a SD below or above reference group means was taken as indicative of a medium effect size and three quarters high.<sup>23</sup> The selection of predictor variables entered into the multivariate analyses was determined by preliminary exploratory analyses, with  $p < 0.05$  used as the threshold for multivariate inclusion. Power was calculated on the basis of 0.75 standardised mean deviation representing clinical relevance on both the neuropsychological (WPPSI and NEPSY) and behavioural (CBCL) measures. For the four-group neuropsychological comparisons, this required a sample size of 76 to attain power of 0.8, and a sample size of 80 for the five-group behavioural comparisons. The actual sample included was 90.

## RESULTS

### Neuropsychological outcomes

Table 1 summarises the mean (SD) scores and clinical effect sizes, on the 10 neuropsychological domains outlined above. As cohort means for “normals” on these scales have tended to increase by several points across time,<sup>24</sup> the extent of these deviations from clinical norms (from 1998 for NEPSY and 1989 for WPPSI) is likely to be a conservative estimate. All four CHD survivor groups showed medium to high effect size deviations from reference group norms on the sensorimotor dimension. Otherwise, both acyanotic groups, regardless of cardiopulmon-

**Table 1** Mean neuropsychological domain scores (standard deviation) across the four congenital heart disease survivor groups

Dimension	Acyanotic-closed (n = 34)	Acyanotic-open (n = 25)	Cyanotic-corrected (n = 19)	Cyanotic-complex (n = 12)
Attention*	101.7 (9.7)	98.5 (11.4)	99.1 (10.6)	95.4 (18.2)
Language*	98.9 (15.3)	101.8 (14.1)	97.3 (11.6)	92.5 (11.6)†
Sensorimotor*	89.7 (16.8)†	89.2 (14)†	80.6 (12.8)‡	86.1 (14.5)‡
Visuospatial*	101.3 (15.6)	100 (13.1)	92.4 (14.5)†	96.2 (10.4)
Memory*	95.3 (15.7)	100.7 (12.2)	94.9 (11.1)	96.1 (14.4)
Verbal reasoning§	8.7 (3)	9.6 (1.7)	7.8 (2.5)‡	8.8 (3.4)
Non-verbal reasoning§	9.7 (2.6)	9 (2.5)	8.1 (3.3)†	9.6 (2.4)
Social reasoning§	8.8 (2.5)	9.9 (1.9)	8.1 (2.3)†	8.7 (2.3)
Cognitive speed§	8.7 (2.7)	8.7 (2.6)	9.6 (3.1)	9.6 (2.7)
Number skills§	8.8 (2.7)	9.3 (2.3)	7.9 (2.9)†	7.9 (2)†

\*Developmental neuropsychological assessment (NEPSY) tests: reference group mean 100 (SD 15).

†Study group mean is at least half a SD below reference group mean, defined as a medium effect size.

‡Study group mean is at least three quarters of a SD below reference group mean, defined as a large effect size in terms of clinical significance.<sup>25</sup>

§Wechsler Preschool and Primary Scale of Intelligence (WPPSI) tests: reference group mean 10 (SD 3).

ary bypass surgery, had all other neuropsychological competencies within the normal range.

The cyanotic groups, both of whom underwent open-heart surgery, showed a greater number of clinically relevant effect size deviations—on six of the domains in the cyanotic-corrected group and on three domains in the cyanotic-complex group. No evidence was suggested, therefore, that neuropsychological outcomes are worse in children with cyanosis with palliation only. Although the data suggest a clinical pattern of increasing problems being associated with cyanosis, regardless of corrective status, multivariate analyses of variance did not indicate significant differences among the four groups across all 10 dimensions together (Pillai's trace  $F = 1.03$ ;  $p = 0.4$ ).

For multivariate analyses, two neuropsychological factors (accounting for 56% of the variance) were extracted by principal component analysis: (1) a perceptual-motor skills factor included non-verbal reasoning, sensorimotor, visuospatial, cognitive speed and number skills; (2) a verbal skills factor included social reasoning, memory, verbal reasoning and language dimensions. Two multivariate analyses were subsequently conducted, with cyanotic status (cyanotic/acyanotic) and surgical procedure (open/closed) entered as primary variables of interest in both. The univariate criteria for inclusion of other variables are described above, and checks were completed to ensure that no other factors became statistically significant once these were accounted for (supplementary table B). Considering both regressions together, four factors emerged as important determinants for neuropsychological outcomes (supplementary table B). These were paternal education, sex, surgical procedure and a parenting style variable, parental efficacy. Being male and having a father with relatively reduced educational qualifications were the greatest risk factors for poorer performance on the perceptual skills dimension. Open-heart surgery and low efficacy in parent management skills were risk factors for poorer performance on the verbal skills dimension.

### Behavioural outcomes

For behavioural outcomes, data from a mild-control group were available and included as described above. Table 2 summarises the mean (SD)  $t$  scores, together with the percentage in each group whose  $t$  scores on the total problem index were in the range of likely clinical significance ( $t > 60$ ).<sup>17</sup>

The frequency of clinically relevant  $t$  scores in the mild-control group in this study is comparable to those referenced for "normals" in the standardisation sample.<sup>17</sup> Frequencies are comparable in both acyanotic groups, but seem to vary between

the cyanotic groups—being twice as high in the cyanotic-complex group and reduced in the cyanotic-corrected group. An overall significant difference was seen in mean scores across groups ( $F = 2.95$ ;  $p = 0.02$ ), although retrospective Tukey tests did not suggest any significant pairwise comparisons ( $p > 0.05$ ) to indicate the specific source of this difference. Inspection of means and clinical frequencies suggest that the most likely interpretation is of comparable, or reduced, levels of behaviour problems in the cyanotic-corrected group compared with the mild-control group, and raised levels in the other groups, but most clearly in the cyanotic-complex group.

Group comparisons clearly do not suggest a simple additive effect of cyanosis and surgical procedure as risk factors for poorer behavioural adjustment. A multivariate analysis, which incorporated these disease and surgical factors, but which also included the family and cognitive factors described above, was conducted. This was conducted for the four study groups of interest only because (1) relative comparisons of disease, surgical and maternal worry about illness did not apply to the mild-control group and (2) it was the relative importance of these disease and surgical factors versus psychosocial factors that was of interest. As the preliminary univariate analyses suggested that many more psychosocial factors contributed to behavioural outcomes than was found for the neuropsychological outcomes, a backward regression analysis was conducted in this case to derive the most parsimonious final regression model. The final model indicated that five factors were statistically significant; together, these accounted for 59% of the variance on behavioural outcomes (supplementary table C). These were parenting style (parental control), marital status, maternal worry, cyanotic status and maternal mental health. Specifically, risk factors for poorer behavioural adjustment included poor parental control skills, lone parent status, high maternal worry about the child, and raised levels of maternal psychological symptoms. Although cyanosis was associated with poorer neuropsychological outcomes, acyanotic status was more of a risk factor for behavioural outcomes. Neither surgical procedure nor length of time on bypass contributed to outcomes here.

## DISCUSSION

### Group comparisons

Group profiles provide some evidence that children with cyanosis who have undergone open-heart surgery are at greater risk of generally poorer neuropsychological outcomes than children without cyanosis. However, this risk does not seem to be exacerbated by having a complex cyanotic condition with

**Table 2** Group outcomes on the Child Behaviour Checklist Total Problem Index Score

Scale	Acyanotic-closed (n = 34)	Acyanotic-open (n = 25)	Cyanotic-corrected (n = 19)	Cyanotic-complex (n = 12)	Mild-control (n = 19)
Total Problem Index Score	53.7 (10.9)	52.3 (13)	45.4 (7.8)	54.2 (9.7)	45.6 (13.6)
Percentage in clinically significant range	21	20	5	33	16

Values are mean (SD).

palliative interventions only. This may suggest that the key neurodevelopmental period in the association between cyanosis and compromised cognitive functioning occurs at the prenatal, early postnatal or surgical stage.<sup>25</sup> Concern that ongoing cyanosis across development exacerbates this risk<sup>26</sup> is not substantiated by the group patterns evident in table 1.

Secondly, group patterns suggested that all children with a history of severe CHD, regardless of surgical procedure or cyanotic status, are at risk of sensorimotor problems. This finding suggests that cyanosis is not the only important factor in operation in explaining neuropsychological outcomes after CHD. Generally, heart defects may be a marker for other neurological deficits related to sensorimotor ability.<sup>25</sup> Alternatively, environmental pathways involving reduced stimulation and physical restrictions on movement, created by physical limitations or indeed by an anxious parent, at a key period in infancy may compromise the later development of these skills.

Although associated with poorer neuropsychological outcomes, cyanosis in itself did not seem to be associated with poorer behavioural adjustment as previous research has suggested.<sup>10</sup> Indeed, the pattern of results found in this study highlight the importance of differentiating cyanotic samples by repair status. Findings suggested that the cyanotic-corrected group had fewer behaviour problems than the acyanotic and mild-control groups. In comparison, the cyanotic-complex group had statistically the highest mean score on the CBCL, and the highest frequency of clinically relevant scores. Childhood survivors of CHD with ongoing medical, physical

and associated psychosocial challenges seem to be most at risk of behavioural difficulties.

### Multivariate determinants of risk

The multivariate analyses of outcome have highlighted that the relevance of disease and surgical factors must be considered within a wider, systemic, context. The relative size and statistical significance of the  $\beta$  coefficients of predictor variables in the final regression models for both neuropsychological and behavioural outcomes (supplementary tables B and C) suggest that, although cyanotic and surgical factors have aetiological relevance, family and social variables make an often greater contribution to risk and outcome. Especially when considering behavioural outcomes, parenting style, marital status and maternal mental health difficulties are seen to have greater predictive importance than the disease factor of cyanosis (supplementary table C). Maternal worry about the child also exerts a considerable effect. Although neuropsychological outcomes might be expected to be less influenced by environmental processes, even here, parenting style, paternal education and sex exerted at least a comparable influence to the surgical procedure variable in predicting outcomes. Such findings place the effect of disease and surgical factors on subsequent child adjustment in a psychosocial context.

### Clinical implications

In addition to informing prognosis, these findings have important implications for intervention. It may be difficult or impossible to change many of the disease, surgical and social variables of importance documented above (eg sex, marital status and educational level in the family). However, for some of the other risk factors described above—maternal worry, mental health difficulties and parenting style—early interventions of a psychological nature may improve outcomes.<sup>27</sup> Moreover, the sensorimotor difficulties evidenced by all groups may suggest that some form of movement treatment or sensory integration may be useful.<sup>28</sup> A clinical trial that tests these propositions is under way at this centre.

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### What is already known on this topic

- Contradictory evidence in studies using restricted defect or surgical samples suggests that children with congenital heart disease may be at risk of negative neuropsychological and behavioural outcomes.
- Knowledge is limited on how important surgical and cyanotic factors are in predicting these in comparison with psychosocial and familial influences.

### What this study adds

- Cyanosis and open-heart surgery together lead to compromised neuropsychological outcomes, but this does not seem to be exacerbated by having an uncorrected, palliative, status—the latter does, however, tend to be associated with worse behavioural outcomes.
- Family factors may be more important than disease factors in predicting behavioural outcomes especially.
- Sensorimotor delays in early childhood may occur for these children regardless of cyanosis or open-heart surgical status.



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## ARCHIVIST

### Hip dislocation in severe cerebral palsy

In recent years, it has been recommended that the management of children with bilateral spastic cerebral palsy should include close attention to the hips, with radiological surveillance of at-risk hips to detect subluxation and early intervention with postural management and surgery. A report from Derby, UK (Richard Morton and colleagues. *Develop Med Child Neurol* 2006;**48**:555–8), has provided data on hip dislocation among children with bilateral spastic cerebral palsy who were managed conventionally before modern, more active management was introduced.

The retrospective case note study included 110 children (62 boys) who attended special schools in southern Derbyshire between 1985 and 2000. The children were grouped according to severity on the Gross Motor Function Classification System (GMFCS), levels II–V. The proportion of dislocated hips increased with age and disease severity. Of the 18 children at GMFCS level II, none had a hip dislocation up to age 15 years, but preventive operations were performed on six hips. Of the 16 children at GMFCS level III, none had dislocations at ages 5 and 10 years, but one had a hip dislocation at age 15 years. Preventive operations were performed on 13 hips. The one hip became dislocated after operations at ages 4 and 6 years. Of the 35 children at GMFCS level IV, three children had dislocations at age 5 years (one bilateral), seven at age 10 years (one bilateral) and eight at age 15 years (two bilateral). Twenty hips were operated on, and three of these later dislocated. Of the 41 children at GMFCS level V, 9 (four bilateral), 16 (four bilateral) and 12 (three bilateral) children had dislocation at ages 5, 10, and 15 years respectively. In all, 30 hips were operated on and 10 dislocated later. Altogether 38 hips dislocated in 30 children. Preventive surgery seemed to be successful in many children. Morton *et al* believe that orthopaedic referral was often made too late, usually after dislocation had occurred. No preventive surgery had been performed for 42% of the children with dislocation, and 21% of hips undergoing preventive surgery went on to be dislocated. These data are presented as a baseline against which the results of current management can be judged.